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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/541,844	04/03/2000	Jacob S. Tou	SO-3181-00-US	4246

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EXAMINER	
WEBER, JON P	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 05/13/2002 13

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/541,844	TOU ET AL.	
	Examiner	Art Unit	
	Jon P. Weber, Ph.D.	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 March 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 5-21* is/are pending in the application.

4a) Of the above claim(s) *15-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 5-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Status of the Claims

The response with amendments filed 08 March 2002 has been received and entered. Claims 1-3 and 5-21 have been presented for examination.

Election/Restrictions

Claims 15-21 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Group, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 6, file 13 July 2001. It is suggested that the non-elected claims be canceled to expedite prosecution.

Claim Rejections - 35 USC § 102

The rejections under 35 USC 102(e) over Blumberg et al. (US 5,763,215) or Pedersen et al. (US 5,783,413) are withdrawn in view of the incorporation of the limitations of claim 4, not rejected under this statute, into claim 1. The arguments will be addressed *infra*.

Claim Rejections - 35 USC § 103

Claims 1-3 and 5-14 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Blumberg et al. (US 5,763,215) and Pedersen et al. (US 5,783,413) in view of Harper et al. (US 4,900,673) and Obata et al. (JP 07,289,256) or Obata et al. (1997).

It is argued that Blumberg et al. (US 5,763,215) do not exemplify removing Ala from bGH, this is a speculative position, and do not explain the lack of removing Ala from HSOD in

example X. Hence, it is argued that Blumberg et al. (US 5,763,215) teaches away from the claimed invention.

Blumberg et al. (US 5,763,215) disclose using exactly the same aminopeptidase as instantly claimed, to remove N-terminal amino acids. The focus of Blumberg et al. (US 5,763,215) is on removing Met which occurs on proteins produced recombinantly in bacteria and does not occur on the naturally occurring protein. The removal of Leu is also exemplified. Blumberg et al. (US 5,763,215) state that for bGH, after the Met is removed, Ala may also be removed. This is a teaching that Ala can be removed. It is not speculative. The instant disclosure removes Ala from hGH, the human cognate of the bovine molecule disclosed by Blumberg et al. (US 5,763,215).

Aminopeptidase is a processive enzyme. That is, every time an amino acid is removed from the amino terminus, a new amino terminus is formed which itself may be removed by the aminopeptidase. This is the meaning of the passage in Blumberg et al. (US 5,763,215). The processivity of the aminopeptidase will continue until an amino acid which "blocks" further reaction is encountered. Blumberg et al. (US 5,763,215) indicates that Pro, Asp, Glu and Phe-Pro are suitable stopping signals. The ability to remove additional amino acids on the peptide will depend on a factors such as the rate of reaction and concentration of peptide with a particular amino terminus. Thus, one should obtain a set of progressively shorter chain length peptides if processing is allowed to proceed sufficiently. One can glean from Blumberg et al. (US 5,763,215) that this aminopeptidase can remove Met, Ala and Leu. These amino acids are recognized in the art to be small aliphatic amino acids. A person of ordinary skill in the art would

ascertain from Blumberg et al. (US 5,763,215) that this aminopeptidase should remove other small aliphatic amino acids, Gly, Val and Ile, with a reasonable likelihood of success.

The observation that hSOD is not processed was not discussed further by Blumberg et al. (US 5,763,215). However, since Blumberg et al. (US 5,763,215) used exactly the same enzyme in exactly the same way as instantly, if Blumberg et al. (US 5,763,215) is not enabled, then the instant application is not either. On the contrary, a reasonable explanation, albeit not explicitly proferred by Blumberg et al. (US 5,763,215), is that the amino terminus on hSOD was not accessible to the aminopeptidase. At column 2, lines 22-26 Blumberg et al. (US 5,763,215) recites "It appears that mature eucaryotic proteins are "locked" into a conformation such that the N-terminus is inaccessible to the aminopeptidase." The hSOD used by Blumberg et al. (US 5,763,215) is a mature eurkaryotic protein. Thus, the failure to remove Ala in this case suggests that there are non-working embodiments within the broad scope of the "proteins". However, applicants, as well as the prior art, are allowed to have a certain number of non-working embodiments, so long as a skilled artisan would have a reasonable expectation of success, *In re Marzocchi, 439 F.2d 220, 169 USPQ 367 (CCPA 1971).*

Accordingly, there is no reason to believe that Blumberg et al. (US 5,763,215) teaches away from the instantly claimed invention.

It is argued that Pedersen et al. (US 5,783,413) only discuss a multistep enzymatic process for producing a desired protein, where the precursor is an N-terminal extended protein, Aa-Gln-protein and never disclose removing Ala from a protein where the next amino acid is not Gln. It is argued that Pedersen et al. (US 5,783,413) do not provide specific guidance on conditions.

Pedersen et al. (US 5,783,413) discloses that AAP (*Aeromonas proteolytica* aminopeptidase), like other aminopeptidases, is a processive enzyme that removes N-terminal groups until one of: 1) an amino group is blocked, 2) removal is on the N-terminal side of Pro, or 3) the N-terminal Aa is Pro, Glu or Asp (column 3, lines 8-12). The enzyme is apparently fairly non-specific with respect to the amino acids it removes, so long as the amino acid is not proscribed. The combination of enzymes is provided with the express purpose of taking advantage of scenario 2 and 3 above. The aminopeptidase removes the extension up to the Gln, then the cyclase converts Gln into pyroGlu. The final enzyme can remove the pyroglu in a separate reaction. The first two enzyme are used simultaneously or sequentially. In Example 9, a 12-residue tag is removed from TNFα by means of AAP and DAP-I in a processive manner at a pH value of 6.2 for 90 min at 37°C. Within the sequence that is removed is an Ala. Hence, there was a protein with Ala at the N-terminus from which Ala was removed during the processive action of AAP and DAP-I. It cannot be determined which of the two enzymes removes Ala, but both may.

It is argued that Obata et al. (JP 07,289,256) or Obata et al. (1997) are relevant to aminopeptidase from *Aeromonas salmonificidia* not *proteolytica*. It is urged that the properties of enzyme from *salmonificidia* may not be extrapolated to the aminopeptidase from *proteolytica*. However, this argument is not supported by evidence. It is well-known in the art of enzymology that closely related organisms produce similar enzymes with similar activities and specificity. Hence, trypsin from bovine and human are reasonably compared. The two organisms here are from the same genus and would be considered to be more closely related than human and bovine.

Hence, the enzyme properties would be expected to be more similar than human and bovine. Accordingly, absent evidence to the contrary, the argument is not persuasive.

Harper et al. (US 4,900,673) was cited solely for the proposition that the action of AAP to remove Met from proteins (the same reaction which Blumberg et al. focused upon) occurs readily at pH 7.2 in phosphate buffer. The response does not take issue with Harper et al. (US 4,900,673).

Applicant's arguments filed 08 March 2002 have been fully considered but they are not persuasive. The rejection under 35 USC 103 is adhered to for the reasons of record and the additional reasons above.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon P. Weber, Ph.D. whose telephone number is 703-308-4015. The examiner can normally be reached on daily, off 1st Fri, 9/5/4.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 703-308-4743. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Jon P. Weber, Ph.D.
Primary Examiner
Art Unit 1651

JPW
May 7, 2002